IN-LINE UV-VIS SPECTROSCOPY IN SMALL SCALE EXTRUSION AS PROCESS ANALYTICAL TECHNOLOGY DURING EARLY STAGE DEVELOPMENT OF AMORPHOUS SOLID DISPERSIONS

J. Winck[1], M. Daalmann[1], M. Thommes[1]

[1] TU Dortmund University; Emil-Figge-Str. 68; Dortmund / Germany; judith.winck@tu-dortmund.de

ABSTRACT

The poor solubility of a large number of active pharmaceutical ingredients (API) is a major challenge in pharmaceutical research. Therefore, the extrusion of amorphous solid dispersions (ASDs) is one promising approach to enhance the dissolution rate by molecularly dissolve the API in an amorphous carrier polymer. During ASD development, crucial parameters as the dissolution and the decomposition need to be monitored. Within this study, a small scale twin screw extruder was coupled with special ColVisTec UV-Vis probes that are characterized by their small dimensions. This setup enables a systematic formulation development and optimization based on in-line monitoring of crucial parameters using small amounts of material.

Keywords: hot melt extrusion (HME), micro compounder, formulation development, process analytical technology (PAT), UV-Vis spectroscopy

INTRODUCTION

A large number of the active pharmaceutical ingredients (API) that are on the market and the majority of those currently under development have a low solubility [Rodriguez-Aller, 2015]. However, the dissolution process is crucial for the systematic absorption of the active ingredient in the human body. A low solubility of APIs therefore often leads to a low bioavailability and thus an insufficient efficacy.

A common approach to improving bioavailability is to increase the rate of dissolution of the API by administering it in the amorphous state in which the energy to overcome the crystal lattice has already been applied. For the kinetic stabilization of the amorphous state, the active ingredient is embedded in an amorphous carrier polymer with high viscosity, creating an amorphous solid dispersion (ASD) [Vasconcelos, 2007].

Hot melt extrusion (HME) enables a solvent-free production of ASDs by mixing and dispersing processes inside the extruder. In order to process the highly viscous polymers, extrusion processes are usually carried out at elevated temperatures. Furthermore, the solubility temperature has to be reached, which states the minimum required temperature for a specific API content to be soluble in the carrier polymer. However, extrusion at elevated temperatures can cause mechanical as well as thermal decomposition, especially if polymer or API molecules are thermally unstable [Matić, 2020].

In ASD development, this interplay of completely dissolve the API and simultaneously avoid decomposition is a major challenge. Therefore, appropriate process conditions need to be identified during early stage process development. Within this study, the integration of an in-line UV-Vis spectrophotometer during small scale extrusion of ASDs is evaluated in order to develop a fast-working method to optimize process conditions based on reduced material consumption.

RESEARCH CONCEPT

Materials

Two formulations with different drug loads were investigated. Griseofulvin (GRI) (Fagron, Rotterdam, Netherlands) and Itraconazole (ITR) (Ria International India Pvt Ltd, Madurai, India) were used as model drugs.

https://doi.org/10.24355/dbbs.084-202110270940-0

Copovidone (PVPVA) (Plasdone S-630, Ashland Inc., Switzerland) was used as carrier polymer.

Extrusion

The extrusion was carried out using a DSM xplore micro compounder (Xplore Instruments BV, Sittard, Netherlands), a laboratory scale extruder with two intermeshing conical screws, a capacity of about 5 ml, and a die diameter of 3 mm. An air-cooled hopper was used in order to prevent the materials from sticking. 3 g of formulation were fed into the extruder, respectively. The screw speed was set to 50 rpm throughout the whole study. The residence time of the material was set by operating the extruder in the recirculation mode. Therefore, the valve between the screw tips and the die was turned to the recirculation channel and opened immediately after the desired residence time. The material temperature was adjusted by the barrel temperature and calibrated beforehand by using a Testo 875 IR camera (Testo SE & Co. KGaA, Lenzkirch, Germany).

A systematic parameter study was performed for three different drug weight fractions w, as listed in Table 1. Seven different temperatures in specific distance ΔT to the expected solubility temperature T_s were selected [Gottschalk, 2021]. For each temperature, the extrusion was performed with three different residence times t in order to investigate its influence in addition.

Table 1: Process conditions during the extrusion of GRI/PVPVA and ITR/PVPVA.

Parameter	Unit	Values
w (GRI/PVPVA)	[-]	0.15, 0.20, 0.25
w (ITR/PVPVA)	[-]	0.25, 0.30, 0.35
Residence time	[min]	1, 3, 10
ΔT to T_s	[K]	-10, -7, -3, 0, 3, 7, 10

Optical analysis

The presence of remaining drug crystals and coloring was investigated by a visual method. Therefore, the extrudates were placed on a black background and besides a yellowish coloring it was detected, whether they are transparent or opaque. Thereby, a transparent extrudate was assessed as an amorphous solid dispersion whereas an opaque extrudate was considered to contain unresolved crystals.

UV-Vis spectroscopy

The in-line UV-Vis spectroscopy was performed with an Inspectro X spectrophotometer (ColVisTec, Berlin, Germany) in the transmission mode. Due to the small dimensions of the extruder and the die channel a special pair of ColVisTec probes was implemented into the experimental setup that differ from the standard TPMP probes. A range of 224 to 820 nm and a sampling rate of 1 Hz was chosen. The obtained spectra were calibrated by using spectra of the pure polymer as a blank reference.

RESULTS AND DISCUSSION

In addition to the optical analysis and transmission spectra (data not shown), the extrusion of ADSs is evaluated based on the L* and b* value of the CIELAB color specification system. More specifically, the lightness increases with an increasing L* value, indicating the API dissolution in the polymer. Color changes from blue to yellow are represented by the b* value.

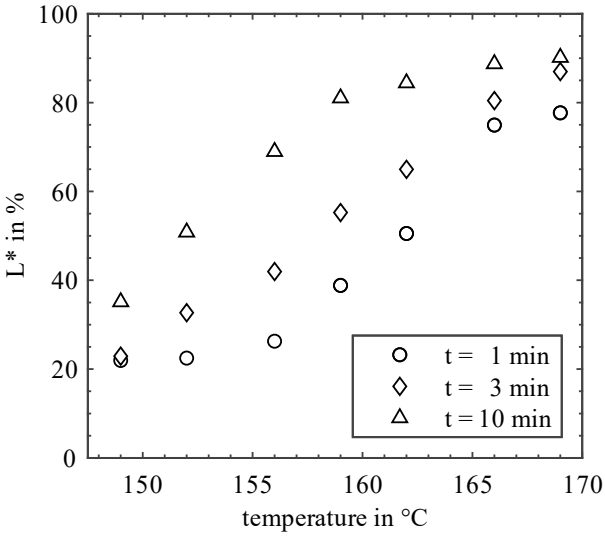

Figure 1: L* value of GRI/PVPVA/0.15 as a function of temperature and residence time.

Exemplary results shown for GRI/PVPVA/0.15 in figure 1 clearly indicate that the L* value increases with increasing temperature. In addition, an increase in the L* value with increasing residence time can be seen for a certain temperature. In particular at the temperatures of 156 °C, 159 °C and 162 °C, the major changes of L* values for different residence times can be found in comparison to the other temperatures. This shows that by reaching the solubility temperature of 159 °C and in a small temperature range of 3 °C below and above the

https://doi.org/10.24355/dbbs.084-202110270940-0

solubility temperature, an increasing lightness occurs. Here, the active ingredient is increasingly dissolved in the carrier polymer, so that the crystalline components decrease and the lightness increases as a result.

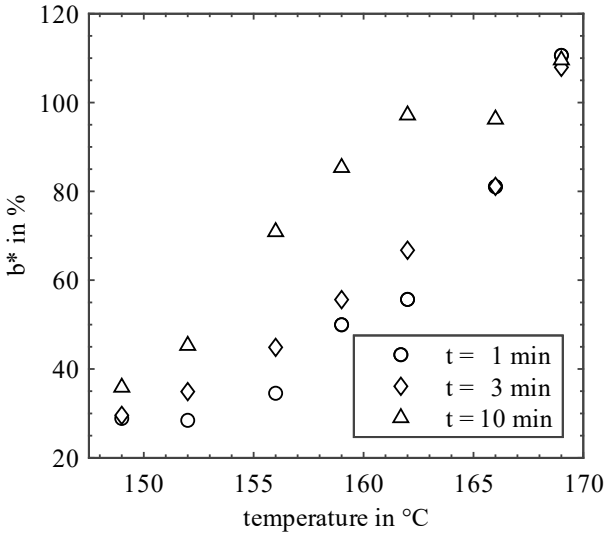

Figure 2: b* value of GRI/PVPVA as a function of temperature and residence time.

Figure 2 shows the influence of the residence time and the temperature on the b* value for GRI/PVPVA/0.15. An increase in the b* value can be seen for both increasing temperatures and increasing residence times. This is caused by an increasing thermal and mechanical stress resulting in material decomposition and thus a yellow or brown discoloration of the ASDs. Similar trends were also obtained for the other formulation ITR/PVPVA as well as for any drug weight fraction (data not shown).

CONCLUSIONS

A special UV-Vis probe, which measures low material quantities inside the small scale extruder, was integrated into the process. Based on a comparison with an optical inspection of the extrudates, the suitability of the in-line UV-Vis spectroscopy was confirmed. With the transmission spectra and the lightness value L*, remaining crystalline components were detected and thus the formation of ASDs could be assessed. Since color values were also determined, conclusions regarding the material decomposition were drawn.

The influence of temperature and residence time on the formation of ASDs was quantified. By comparing the temperature required for dissolution with the temperature of decomposition for a specific API content and residence time, suitable process regimes can be identified to finally optimize the whole process development.

ACKNOWLEDGMENT

The authors thank ColVisTec (Andreas Berghaus) and Ashland (Christian Muehlenfeld) for their technical support.

REFERENCES

Gottschalk, T.; Grönniger, B.; Ludwig, E.; Wolbert, F.; Feuerbach, T.; Winck, J.; Sadowski, G.; Thommes, M. (2021): Influence of residence time in manufacturing amorphous solid dispersions via hot melt extrusion. In: Proceedings of the 12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology

Matić, J., Alva, C., Witschnigg, A., Eder, S., Reusch, K., Paudel, A.; Khinast, J. (2020) Towards predicting the product quality in hot-melt extrusion: Small scale extrusion. In: International journal of pharmaceutics: X 2, 100062. DOI: 10.1016/j.ijpx.2020.100062

Rodriguez-Aller, M.; Guillarme, D.; Veuthey, J.-L.; Gurny, R. (2015) Strategies for formulating and delivering poorly water-soluble drugs. In: Journal of Drug Delivery Science and Technology 30, 342–351. DOI: 10.1016/j.jddst.2015.05.009

Vasconcelos, T.; Sarmento, B.; Costa, P. (2007): Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. In: Drug discovery today 12, 1068–1075. DOI: 10.1016/j.drudis.2007.09.005